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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,916	10/02/2000	Carl Anthony Blau	UOFW115624	4343

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/582,916	BLAU ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *43,54,67-69 and 77-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42,44-53,55-66 and 70-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/11/05 has been entered. As requested, applicant's amendment and the third declaration under 37 CFR 1.132 by Dr. Blau filed concurrently with the RCE have been entered. Claims 1-88 are pending in the instant application. This application contains claims 43, 54, 67-69, and 77-88 drawn to an invention nonelected without traverse in Paper No. 12. Claims 1-42, 44-53, 55-66, and 70-76 are currently under examination. The applicant is further reminded that the species election of "hematopoietic stem cells" still stands, although the claims have not been so limited. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Rejections - 35 USC 102

The rejection of claims 1-42, 44-53, 55-66, and 70-76 under 35 U.S.C. 102(e) as being anticipated over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., is

withdrawn in view of applicant's amendments to the claims and the supporting declaration by Dr. Blau under 37 CFR 1.132 (the third Blau Declaration). In regards to the product claims, claims 44-53, and 55, the applicant has amended the claims to include the limitation that the drug-binding domain comprises at least one amino acid change compared to the most prevalent naturally-occurring amino acid sequence. This limitation is not specifically taught by Capon et al. Regarding the method claims, the applicant has added the limitation that the transduced cells are exposed to a concentration of the drug effective to induce association of two or more fusion proteins, thereby inducing growth, proliferation or differentiation of said cells. Applicant's third declaration provided new evidence that "saturating" concentrations of the bivalent drug FK1012 does not result in dimerization of fusion proteins and thus does not induce proliferation of Ba/F3 cells expressing the fusion proteins. As such, since Capon et al., while teaching the administration of the drug to induce proliferation, only suggests testing a "saturating" concentration of the drug to induce proliferation and does not actually demonstrate that such a concentration or any other concentration is effective in inducing the proliferation of a primary cell type, applicant's declaratory data is considered persuasive in overcoming the rejection of record over the method claims as amended.

In view of applicant's amendments to the claims, the following new rejections apply.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-42, 59-66, and 70-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., in view of Blau et al. (1997) PNAS, Vol. 94, 3076-3081.

Capon et al. teaches the transduction of cells with a recombinant nucleic acid encoding 1) a chimeric protein comprising an extracellular inducer-responsive clustering domain capable of binding an extracellular inducer that transmits a signal to a proliferation signaling domain, a transmembrane domain, and a proliferation domain that signals a host cell to divide, or 2) a chimeric protein comprising an intracellular inducer-responsive clustering domain capable of binding an intracellular that transmits a signal to a proliferation signaling domain and a proliferation domain that signals a host cell to divide (abstract, and columns 1-2). In particular,

Capon et al. teaches that the extracellular or intracellular inducer-responsive clustering domain of the chimeric protein is derived from immunophilin, e.g. FKBP, and that the cytoplasmic signal transduction domain is derived from homodimerizing receptors such as G-CSFR, EPO-R, GHR, PRLR, TPOR, and gp130 (Capon et al., columns 7, 9, 13, 15, 34-35, and 42-43). Capon et al. further teaches that cells transduced with an appropriate vector comprising the nucleic acid, such as a viral vector or DNA plasmid, which encodes said chimeric protein can be induced to expand and proliferate by exposing the cells to a multivalent inducer molecule. In the case of chimeric proteins which encode FKBP, Capon et al. teaches that the inducer molecule is a multivalent cell-permeant drug with a molecule weight of less than 5 kD such as FK1012 (Capon et al., columns 15, 19, 21 and 22). In addition, Capon et al. teaches that target cells for expansion can be transduced *in vitro* or *in vivo* for use in the treatment of human diseases such as cancer or autoimmune disease (Capon et al., columns 1, 16 and 21-22). In regards to cells transduced *ex vivo* and introduced into the host mammal, Capon et al. teaches that the cells can be allogeneic or autologous cells, including hematopoietic stem cells capable of developing into cells of the myeloid and lymphoid lineages (Capon et al., columns 16, and 21-22).

While Capon et al. teaches administering the inducer molecule to the transduced cells in order to stimulate cell proliferation and/or differentiation, Capon et al. does not provide specific guidance for the concentration of inducer to administer in order to achieve cell proliferation. It is noted that in example 11(g), Capon suggests an experiment to test cell proliferation *in vitro* where the cells are contacted with plates coated with a saturating concentrations of an inducer drug, such as FK1012, a concentration which the applicant has demonstrated to be ineffective in inducing proliferation. However, at the time of filing, the optimization of drug concentrations for

dimerization of chimeric proteins was routine and well-developed. In particular, Blau et al. teaches methods to determine the optimal concentration of FK1012 to induce the dimerization of chimeric proteins comprising FKBP and EpoR in cells expressing the chimeric receptor such that the cells proliferate (Blau et al., page 3078, Figures 2 and 3). Further, Blau et al., actually demonstrates concentrations of FK1012 effective to induce the association of the chimeric protein on cells, thereby inducing cell proliferation (Blau et al., Figures 2 and 3). Therefore, in view of the motivation provided by the Blau et al. for testing a variety a concentrations of FK1012 to determine the optimum concentration for inducing the proliferation of cells expressing a chimeric protein comprising FKBP domains and the EpoR signaling domain, it would have been *prima facie* obvious to the skilled artisan at the time of filing to test a variety of concentrations of the inducer drug to determine the optimum concentration for inducing proliferation of cells according to the methods of Capon et al. The skilled artisan would further have had a reasonable expectation of success in identifying the optimum concentration of FK1012 to induce cell proliferation based on the successful demonstration in Blau et al. of the testing methods and the identification of actual concentrations of FK1012 which were effective in inducing cell proliferation in cell expressing the chimeric protein.

In regards to the obviousness of optimizing concentrations, the applicant is also pointed to the MPEP, section 2144.05 which sets forth that, "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' *In re Aller*, 220 F.2d 454, 456, 105

USPQ 233, 235 (CCPA 1955)". See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); and *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969), *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Claims 44-53, and 55-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., in view of U.S. 5,994,313 (11/30/99), hereafter referred to as Crabtree et al., and Blau et al. (1997) PNAS, Vol. 94, 3076-3081.

Capon et al. teaches the transduction of cells with a recombinant nucleic acid encoding 1) a chimeric protein comprising an extracellular inducer-responsive clustering domain capable of binding an extracellular inducer that transmits a signal to a proliferation signaling domain, a transmembrane domain, and a proliferation domain that signals a host cell to divide, or 2) a chimeric protein comprising an intracellular inducer-responsive clustering domain capable of binding an intracellular that transmits a signal to a proliferation signaling domain and a proliferation domain that signals a host cell to divide (abstract, and columns 1-2). In particular, Capon et al. teaches that the extracellular or intracellular inducer-responsive clustering domain of the chimeric protein is derived from immunophilin, e.g. FKBP, and that the cytoplasmic signal transduction domain is derived from homodimerizing receptors such as G-CSFR, EPO-R, GHR,

PRLR, TPOR, and gp130 (Capon et al., columns 7, 9, 13, 15, 34-35, and 42-43). Capon et al. further teaches that cells transduced with an appropriate vector comprising the nucleic acid, such as a viral vector or DNA plasmid, which encodes said chimeric protein can be induced to expand and proliferate by exposing the cells to a multivalent inducer molecule. In the case of chimeric proteins which encode FKBP, Capon et al. teaches that the inducer molecule is a multivalent cell-permeant drug with a molecule weight of less than 5 kD such as FK1012 (Capon et al., columns 15, 19, 21 and 22). In addition, Capon et al. teaches that target cells for expansion can be transduced *in vitro* or *in vivo* for use in the treatment of human diseases such as cancer or autoimmune disease (Capon et al., columns 1, 16 and 21-22). In regards to cells transduced *ex vivo* and introduced into the host mammal, Capon et al. teaches that the cells can be allogeneic or autologous cells, including hematopoietic stem cells capable of developing into cells of the myeloid and lymphoid lineages (Capon et al., columns 16, and 21-22).

Capon et al. differs from the instant invention by not teaching that the inducer-responsive clustering domain (ICD) of the chimeric protein comprises at least one amino acid change compared to the most prevalent naturally-occurring amino acids sequence. However, Capon et al. does suggest that modifications can be made to the ICD to create improved receptor-ligand binding (Capon et al., column 5, lines 12-15). Further, at the time of filing, various modifications to FKBP12s were known which increased their affinity or selectivity for their ligand. Crabtree et al. supplements Capon et al. by teaching similar chimeric proteins comprising an inducer-responsive clustering domain and a signaling domain where the inducer-responsive domain of FKBP12 contains specific amino acid changes as compared to the wild type sequences (Crabtree et al., column 23). Therefore, based on the motivation to make modifications to the ICD to create

improved receptor-ligand binding provided by Capon et al., and the teachings of Crabtree et al. for specific single amino acid changes to FKBP12 to improve its binding affinity or specificity to ligand which can be used in chimeric signaling proteins, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use one of the modified FKBP12 domains taught by Crabtree et al. in the chimeric proteins taught by Capon et al.. Further, based on the high degree of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in making expression vectors encoding a chimeric protein comprising a modified FKBP12 and a proliferation signaling domain such as EpoR and in using those vectors to transfect/transduce hematopoietic stem cells according to Capon et al.

While Capon et al. teaches administering the inducer molecule to the transduced cells in order to stimulate cell proliferation and/or differentiation, Capon et al. does not provide specific guidance for the concentration of inducer to administer in order to achieve cell proliferation. It is noted that in example 11(g), Capon suggests an experiment to test cell proliferation *in vitro* where the cells are contacted with plates coated with a saturating concentrations of an inducer drug, such as FK1012, a concentration which the applicant has demonstrated to be ineffective in inducing proliferation. However, at the time of filing, the optimization of drug concentrations for dimerization of chimeric proteins was routine and well-developed. Crabtree et al. for instance teaches various *in vitro* assays which vary the concentration of FK1012 to determine effective concentrations for oligomerizing chimeric receptors comprising FKBP12 and a signaling domain and further teaches methods to optimize dosages of the inducer drug for *in vivo* administration (Crabtree et al., columns 40 and 43-44). In addition, Blau et al. supplements Capon et al. and Crabtree et al. by teaching methods to determine the optimal concentration of FK1012 to induce

the dimerization of chimeric proteins comprising FKBP and EpoR in cells expressing the chimeric receptor such that the cells proliferate (Blau et al., page 3078, Figures 2 and 3). It is also noted that Blau et al. actually demonstrates concentrations of FK1012 effective to induce the association of the chimeric protein on cells, thereby inducing cell proliferation (Blau et al., Figures 2 and 3). Therefore, in view of the motivation provided by both Crabtree et al. and Blau et al. for testing a variety a concentrations of FK1012 to determine the optimum concentration for inducing the dimerization of chimeric proteins comprising FKBP12 and for inducing the proliferation of cells expressing a chimeric protein comprising FKBP domains and the EpoR signaling domain, it would have been *prima facie* obvious to the skilled artisan at the time of filing to test a variety of concentrations of the inducer drug to determine the optimum concentration for inducing proliferation of cells according to the methods of Capon et al. The skilled artisan would further have had a reasonable expectation of success in identifying the optimum concentration of FK1012 to induce cell proliferation based on the successful demonstration in Blau et al. of the testing methods and the identification of actual concentrations of FK1012 which were effective in inducing cell proliferation in cell expressing the chimeric protein.

In regards to the obviousness of optimizing concentrations, the applicant is also pointed to the MPEP, section 2144.05 which sets forth that, "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. '[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' *In re Aller*, 220 F.2d 454, 456, 105

USPQ 233, 235 (CCPA 1955)". See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); and *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969), *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler,* 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-20, and 32-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 32 lack antecedent basis for the limitation "wherein the cells are removed from the mammal". There is no recitation of "a mammal" in claims 1 or 21 upon which claims 12 and 32 depend. Claims 13-18 and 33-38 depend on claims 12 or 32 and thus are included in this rejection.

Claims 19 and 39 lack antecedent basis for the limitation "wherein the cells are transduced within the mammal". There is no recitation of "a mammal" in claims 1 or 21 upon

which claims 19 and 39 depend. Claims 20 and 40 depend on claims 19 or 39 and thus are included in this rejection.

Claim Objections

Claim 57 is objected to because of the following informalities: the claim recites, "A method of claim 56"; however, as a dependent claim, the proper article to begin the claim is "The" not "A". Appropriate correction is required.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because: the executed oath/declaration filed on 10/2/00 states that there are no provisional applications to which the applicant claims priority. However, the applicant amended page 1 of the specification on 2/17/04 to insert a paragraph stating that the applicant claims benefit or priority to US provisional applications 60/070/754, 60/070,893, and 60/102,888.
>
> Appropriate correction is required.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be

reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER